UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/776,935	12/22/1998	JACQUES DUMAS	BAYER 12P1	7400

7590 03/20/2007

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
ARLINGTON COURTHOUSE PLAZA I
2200 CLARENDON BOULEVARD
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
WILLIAMS, LEONARD M	
ART UNIT	**PAPER NUMBER**
1617	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
2 MONTHS	03/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/776,935
Filing Date: December 22, 1998
Appellant(s): DUMAS, JACQUES

Csaba Henter
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12/04/2006 appealing from the Office action mailed 07/03/2006.

(1) Real Party in Interest

The real party in interest is Bayer Pharmaceuticals Corporation.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Goodman and Gilman's, The Pharmacological Basis of Therapeutics, 9th edition, 1996, pg. 51.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 17-24, 26 and 30-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of copending Application No. 09/947761. Although the conflicting claims are not identical, they are not patentably distinct from each other because Claim 17 of the current application is drawn to a method for the treatment of rheumatoid arthritis which comprises administering a compound of formula I wherein formula I is an urea with functionalities A and B. Claim 1 of the '761 application is drawn to a method for treatment of a diseases, other than cancer, mediated by p38, comprising administering a pharmaceutical composition comprising a compound of formula I wherein formula I is an urea with functionalities A and B. Both the current claims and the '761 application

claims define A and B as having equivalent scope and breadth. Further claim 1 of '761 is a broader claim than current claim 17.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-19, 22, 26 and 30-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those

in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). ***The Nature of the Invention***:

The rejected claim(s) is/are drawn to an invention which pertains to the treatment of rheumatoid arthritis with a heterocyclic substituted urea.

(2). ***Breadth of the Claims***:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass a treatment comprising the administration *any* urea encompassed by the formula illustrated by the broad generic structure of formula I. The nature of the invention is complex in that it potentially encompasses a vast number of compounds. For example, when B is phenyl, X is an amide and A is a diazole, R5 and R5' can be independently selected from more than 43 groups; R1 can be selected from 34 groups; and R1' can be selected from 16 groups (which may, in turn, be substituted with more than 100 different groups in various numbers and patterns). A basic look at a single variable of what A, B and Xn (when n is 1) may be leads to variations numbering in excess of (43x43x34x16x100) 100 million possibilities. It is noted that A may be selected from at least 26 groups; B is selected from 3 groups; n is 0-3; and X is selected from at least 88 different groups (many of which may be substituted with the at least 43 groups of R5 and R5').

(3). ***Guidance of the Specification***:

The guidance given by the specification as to what types of ureas would be useful in a method of the instant invention is limited. Applicant discloses 38 different ureas as ureas useful in *inhibiting p38*. The specification does not teach that the scope of the invention is limited to these ureas and the claims do not claim a method of inhibiting p38, however.

(4). ***Working Examples***:

As discussed above, the working examples show 38 compounds that are capable of inhibiting p38. None are shown to be actually effective at treating rheumatoid arthritis.

(5). ***State of the Art***:

Applicant's assessment of the prior art indicates that inhibition p38 has been shown to inhibit cytokine production (e.g. TNFα, IL-1, IL-6, IL-8) and that TNFα has been linked to rheumatoid arthritis. There is no indication that inhibition of p38 invariably inhibits each of the cytokines listed (as each are simply examples), nor is there any indication that the inhibition of p38 would invariably lead to the treatment of rheumatoid arthritis. Even if we were to assume that an inhibition of p38 would lead to the desired inhibition of TNFα, a link between TNFα production and rheumatoid arthritis doesn't mean that any inhibition of TNFα would treat the rheumatoid arthritis. It is

further noted that the specification likewise indicates that TNFα production is linked to numerous other diseases (see pages 2-5 of the specification).

(6). ***Predictability of the Art***:

It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). In the instant case, as discussed above, there is a vast number of compounds encompassed by the claims wherein only 38 of them have been shown to be effective at inhibiting p38. Furthermore, there is no evidence that the compounds actually treat rheumatoid arthritis; it is simply postulated that because these compounds inhibit p38 that they will in turn inhibit TNF□ and that they will in turn treat rheumatoid arthritis.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutical effects, side effects, and especially serious toxicity that may be generated by drug-drug inerteractions when and/or after adminstering to a host (e.g., a human) any compound represented by formula I. See "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed., 1996), page 51 in particular. *Goodman & Gilman* teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse

drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right of page 51) (emphasis added). In the instant case, in the absence of fully recognizing the identity of the member genus herein, one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with many combinations of any compounds having the claimed functional properties in the pharaceutical compositions herein. Thus, the teachings of *Goodman & Gilman* clearly support that the instant claimed invention is highly unpredictable.

(7). ***The Quantity of Experimentation Necessary***:

The specification fails to provide sufficient support of the broad use of any compound represented by formula I. As a result, one of skill in the art would be forced to perform an exhaustive search for the embodiments of any drugs having the function recited in the instant claim suitable to practice the claimed invention. Furthermore, one of skill in the art would have to determine not only which compounds inhibit p38, but which compounds actually treat rheumatoid arthritis.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

(10) Response to Argument

The applicant's state on page 2 of the appeal brief that the office action dated &/3/2006 alleges only a lack of enablement for the treatment of rheumatoid arthritis with the compounds recited in the claims. The examiner respectfully disagrees. While the lack of enablement for the treatment of rheumatoid arthritis with the compounds recited in the claims is one aspect of the lack of enablement rejection, it is by no means the only issue addressed in the enablement rejection of record. Specifically the examiner has set forth that the breadth of the claims greatly exacerbates the nature of the invention in that up to 100 million different compound embodiments are encompassed. Further the guidance of the specification discloses 38 of the possible 100 million compounds in Table 1 (pages 40-44 of the specification). Thus in order to fully determine the enabling scope one of ordinary skill in the art would have to test an inordinate amount of compounds.

In order to clarify, the examiner respectfully points out that Tables 1and 2 include structural data, mass spectral data, TLC data, TLC solvent system data, melting point data and synthetic means data. There is no mention of activity data for any of the compounds in Tables 1 and 2. Further the examiner points out that the two assays performed are an *in vitro* p38 inhibition assay and a LPS induced TNFα production mouse assay. Neither of these assays is specific for rheumatoid arthritis.

The applicant's allege on page 4 of the appeal brief that the office action admits that the specification provides a showing that specific compounds of the invention are effective at inhibiting p38. The examiner points out that in the determination of enablement one must take into account the Guidance of the specification and the

Working Examples (if any) presented in the specification. In the guidance section of the enablement rejection the examiner stated: "Applicant discloses 38 different ureas as ureas useful in *inhibiting p38*." The examiner clearly indicated that the term inhibiting was italicized for emphasis as it is not explicitly clear in the specification that the 38 compounds in Tables 1 and 2 are the ones that have been tested in the p38 assay. Indeed while the examiner has referred to these compounds as being shown to be useful in the p38 assay it is only in the context of pointing out the "working examples" as necessitated by the Wands factors. The examiner wishes to point out that the specification states in the p38 assay that "All compounds exemplified displayed p38 $IC_{50's}$...", not all compounds disclosed in Tables 1 and 2 leaving the range of compounds possibly tested open ended. Further on page 40 of the specification in reference to Tables 1 and 2 it states: "The following compounds have been synthesized according to the General Methods listed above...". Thus Tables 1 and 2 are clearly just disclosing some compounds that have been synthesized. There is no specific indication in the specification that the compounds are the ones tested in the assays.

The examiner respectfully points out MPEP 608.01: "A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date. In re Glass, 492 F.2d 1228, 181 USPQ 31(CCPA 1974).

While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including

proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention.

Specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims.

Markush claims must be provided with support in the disclosure for each member of the Markush group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula.

A complete disclosure should include a statement of utility. This usually presents no problem in mechanical cases. In chemical cases, varying degrees of specificity are required."

The examiner respectfully points out that in the *in vitro* p38 inhibition assay the applicant's state:

"The *in vitro* inhibitory properties of compounds were determined using a p38 kinase inhibition assay."

and later

"All compounds exemplified displayed p38 $IC_{50's}$ of between 1 nM and 10 μM."

The applicant's referral to "all compounds exemplified" does not clearly limit what compounds were tested (all compounds exemplified in the specification or only compounds exemplified in Table 1, etc...). Further the assertion that the compounds exhibited IC_{50s} of from 1nM to 10 μM does not guide one as to what compounds have

activity and as the difference in activity of from 1nM to 10 μM is more than a 1000 fold one would need to know the activity profile of the specific compounds tested in order to understand the scope and breadth of the invention.

The issue is furthered muddled by the LPS induced TNFα production mouse assay as the applicant's state:

"The *in vivo* inhibitory properties of selected compounds were determined using a murine LPS induced TNFα production *in vivo* model."
The applicants do not disclose which "selected compounds" were tested and do not disclose the activity of the "selected compounds".

The examiner respectfully points out that the applicant's did not test the compounds in accepted specific rheumatoid arthritis assays.

In summary the applicants have not specifically described the compounds tested in the p38 assay or LPS induced TNFα production mouse model, they have not correlated the structure of the compounds tested with their relative activity in said assays and they have not tested the compounds in a specific rheumatoid arthritis assay.

The examiner respectfully points out that if one is to interpret Tables 1 and 2 as being the "All compounds exemplified...", then Table 1 discloses only 37 compounds wherein the A portion of the claimed compounds is a substituted 5-tert-butylpyrazolyl component and the B portion of the claimed compounds is a mono or di-substituted benzene ring. Table 2 consists of only one compound, compound 38, which is an urea where the A portion is a substituted tert-butyl-furan component and the B portion is a di-chloro-benzene ring. Thus the claimed compounds of Formula I, which have been

shown to encompass an inordinate amount of compounds, would be represented by only 38 compounds with only 2 distinct cores (37 compounds with the A portion a 5-tert-butylpyrazolyl component and the B portion of the claimed compounds is a mono or di-substituted benzene ring, and 1 compound with the A portion a substituted tert-butyl-furan component and the B portion a di-chloro-benzene ring). Further these compounds, if taken as exemplifying the compounds in the p38 assay and LPS assay, still are not correlated with treating rheumatoid arthritis or any condition as claimed.

In regards to applicant's assertion that there is no overlap of the claimed compounds in the ODP rejection, the examiner respectfully points the applicant's to claim 1 of the '761 application and claim 17 of the current application where, in the broadest reasonable interpretation of the claims, Formula I of the '761 application clearly overlaps Formula I of the current application as both claims are exceptionally broad and encompass nearly any urea with at least one substituted heteroaryl moiety appended to it.

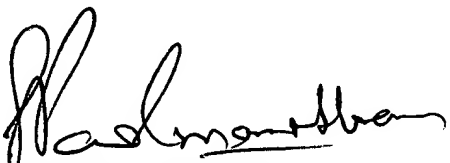
(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Sreenivasan Padmanabhan



SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER

Conferees:

Leonard Williams

Johann Richter

JOHANN RICHTER
SUPERVISORY PATENT EXAMINER
GROUP 1600